App No.: Not Yet Assigned Docket No.: HO-P02514US3 Inventor: Michael D. Schneider, et al. Title: MODULATORS OF Cdk9 AS A THERAPEUTIC TARGET IN CARDIAC HYPERTROPHY

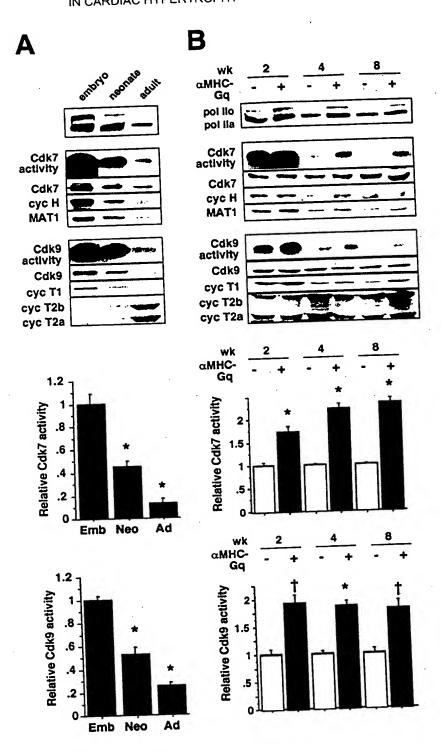


FIG. 1

Inventor: Michael D. Schneider, et al.

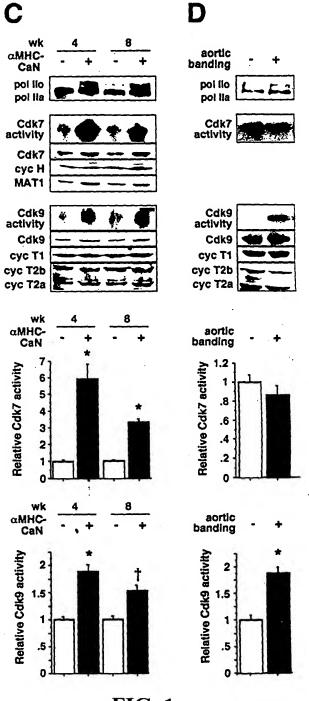
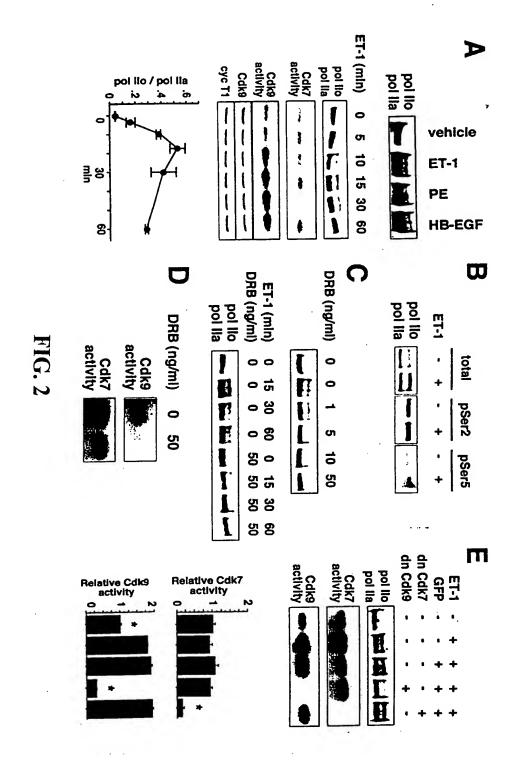


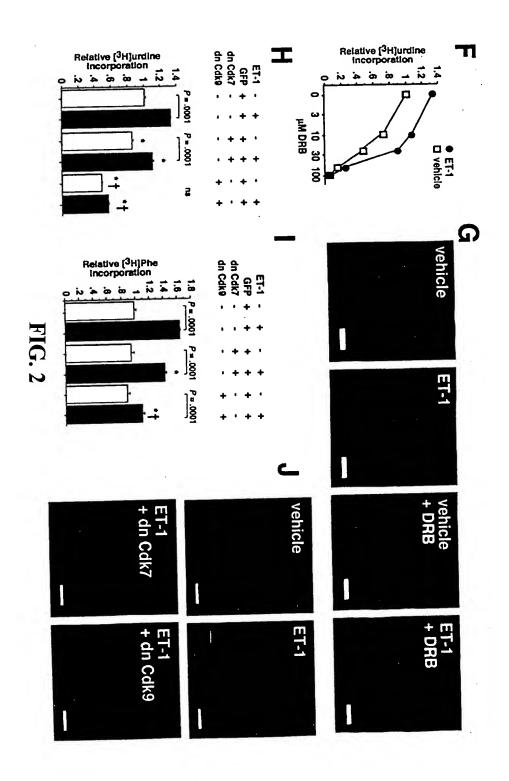
FIG. 1

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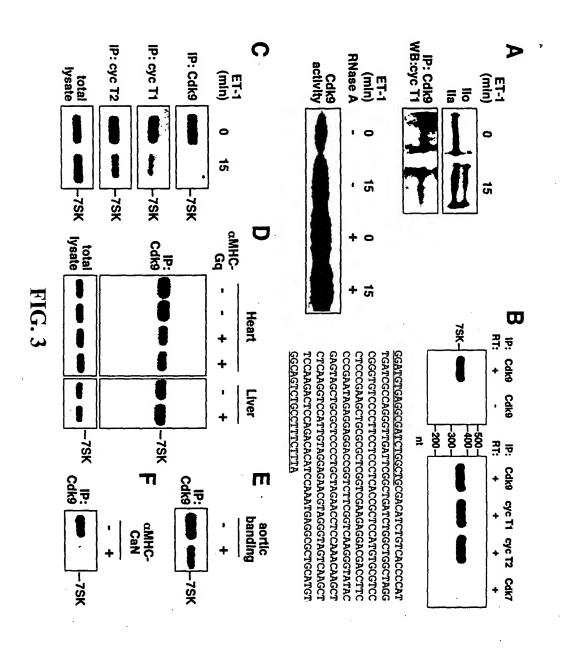
Title: MODULATORS OF Cdk9 AS A THERAPEUTIC TARGET



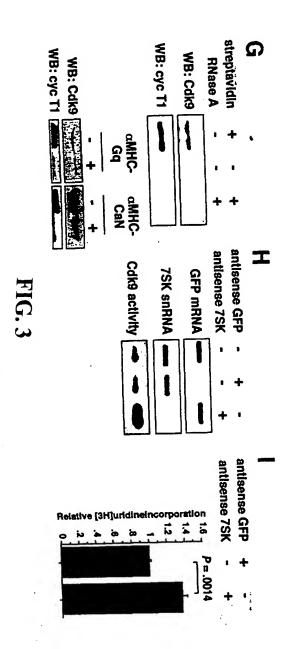
App No.: Not Yet Assigned D. Inventor: Michael D. Schneider, et al. Docket No.: HO-P02514US3



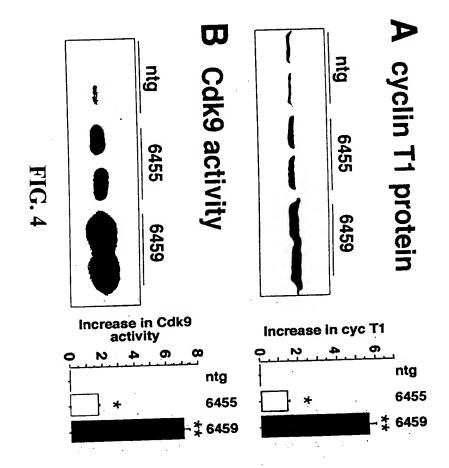
Docket No.: HO-P02514US3 App No.: Not Yet Assigned D. Inventor: Michael D. Schneider, et al.



App No.: Not Yet Assigned Docket No.: HO-P02514US Inventor: Michael D. Schneider, et al.
Title: MODULATORS OF Cdk9 AS A THERAPEUTIC TARGET IN CARDIAC HYPERTROPHY Docket No.: HO-P02514US3

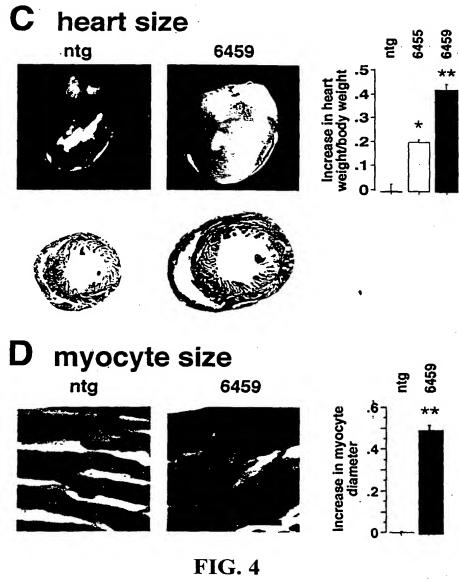


App No.: Not Yet Assigned Diventor: Michael D. Schneider, et al. Docket No.: HO-P02514US3

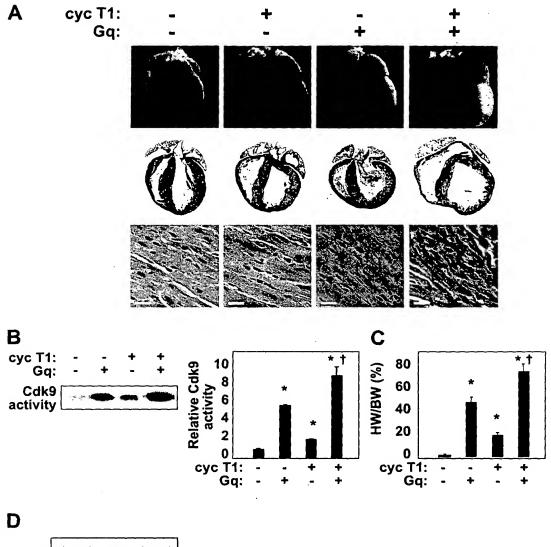


Inventor: Michael D. Schneider, et al.

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Inventor: Michael D. Schneider, et al.
Title: MODULATORS OF Cdk9 AS A THERAPEUTIC TARGET



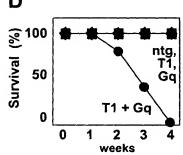


FIG. 5

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Title: MODULATORS OF Cdk9 AS A THERAPEUTIC TARGET IN CARDIAC HYPERTROPHY Docket No.: HO-P02514US3

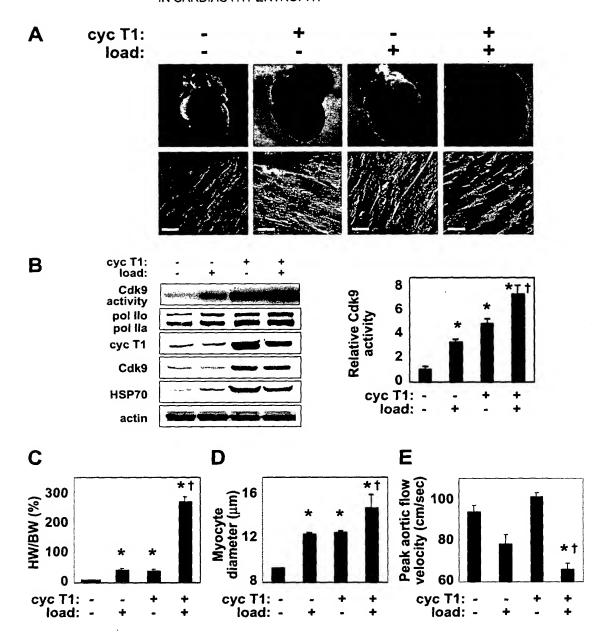


FIG. 6

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Title: MODULATORS OF Cdk9 AS A THERAPEUTIC TARGET

IN CARDIAC HYPERTROPHY



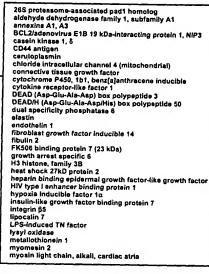


N#25

-3 -2 -1 0 1 2 3

7,12

## INDUCED SYNERGISTICALLY BY CYCLIN T1 + GQ:



nestin NIMA-related kinase 7 PDZ and LIM domain 3
peptidylprolyl isomerase C
peroxiredoxin 4 peroxiredoxin 4
phosphatidylinositol-4-phosphate 5-kinase, type 1 α
phosphotructokinase, platelet
phospholipase A2, group IVA
procollagen, type V, α2; type Vill, α1
prolile 4-hydroxylase, β polypeptide
prostaglandin I2 (prostacyclin) synthase
quaking quaking ras homolog gene family, member J RAS p21 protein activator 3 Rho-associated coiled-coil forming kinase 2 Rho-essociated coiled-coil forming kinase 2 ribonuclease, RNase A family 4 RNA polymerase I associated factor, 53 kD S100 calcium binding protein A6 (calcyclin) sarcoglycan, β scavenger receptor class B, member 2 serpin, clade F, members 1, 2 serpin, clade F, members 1 a serpin dine/spermine H1-acetyl transferase thrombospondin 1 tissue inhibitor of metailoproteinase 3 transforming growth factor. 81 transforming growth factor, β1 troponin I, skeletal, slow 1 vascular cell adhesion molecule 1 WW domain-containing protein 4

## REPRESSED SYNERGISTICALLY BY CYCLIN T1 + GQ:

REPRESSED SYNERGISTICALLY BY C

3-oxoscid CoA transferase
acetyl-Coenzyms A dehydrogenase, short chain
aldo-keto reductase family 1, member B7
alpha-methylacyl-CoA racemase
branched chain ketoacid dehydrogenase E1, β
camitine palmitoyltransferase 2
citrate synthase
creatine kinase, muscle
cyclin-dependent kinase inhibitor 1C (P57)
DEAD/H (Asp-Giu-Ala-Asp/His) box polypeptide 16
dihydrolipoamide branched chain transacylase E2
dihydrolipoamide branched chain transacylase E2
dihydrolipoamide dehydrogenase
dihydrolipoamide S-acetyltransferase precursor
dodecenoyl-Coenzyme A delta isomerase
electron transferring flavoprotein, α
enoyl coenzyme A hydratase 1, peroxisomal
FK506 binding protein 4 (59 kDa)
G elongation factor
gap junction membrane channel protein α1
GrpE-files 1, mitochondrial
heat shock 10 kDa protein 1 (chaperonin 10)
heat shock protein, 60 kDa
inner membrane protein, mitochondrial

Interferon activated gene 203
interferon activated gene 204
isocitrate dehydrogenase 3 (NAD+) α
isocitrate dehydrogenase 3 (NAD+), γ
mitochondrial ribosomal protein L12
mitochondrial ribosomal protein L3
NADH dehydrogenase (ubiquinone) flavoprotein 2
peroxiredoxin 3 peroxiredoxin 3
phospholipid transfer protein
phytanoyl-CoA hydroxylase
potassium voltage-gated channel, Shal-related family,
βrogrammed cell death 8
proteasome (prosome, macropain) 28 subunit, α
retinoid X receptor γ
secreted modular calcium binding protein 2
aeotin 4 septin 4
siabyltransferase 8 (alpha-2, 8-slailyltransferase) D
succinate dehydrogenase complex, subunit A
succinate-Coenzyme A ligase, ADP-forming, β subunit
succinate-Coenzyme A ligase, GDP-forming, β subunit
tetranectin (plasminogen binding protein)
tetranscription elongation factor A (Sill), 3
transclocator of inner mitochondrial membrane 44

FIG. 7

App No.: Not Yet Assigned Docket No.: HO-P02514US3 Inventor: Michael D. Schneider, et al. Title: MODULATORS OF Cdk9 AS A THERAPEUTIC TARGET

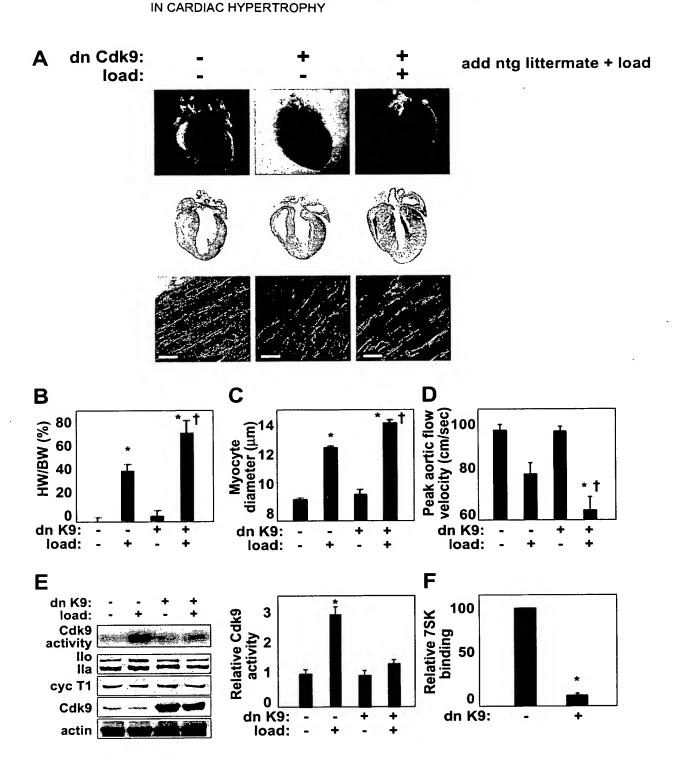
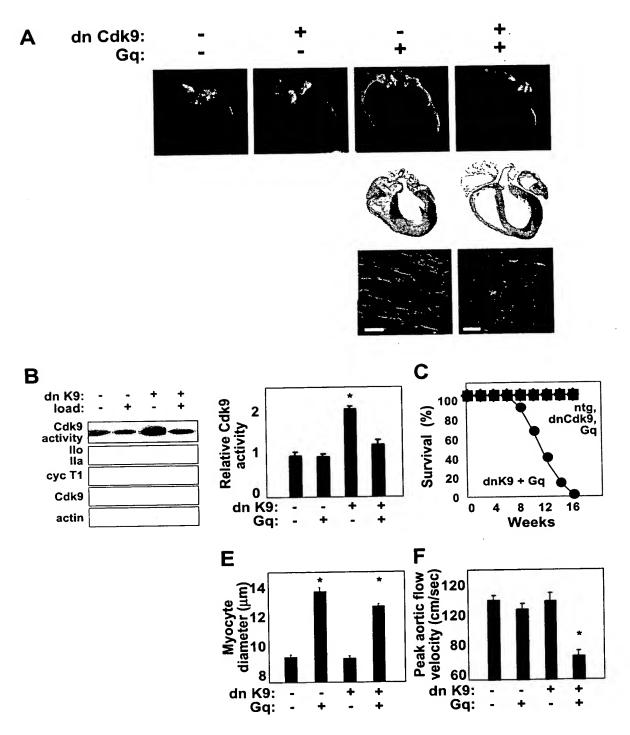


FIG. 8

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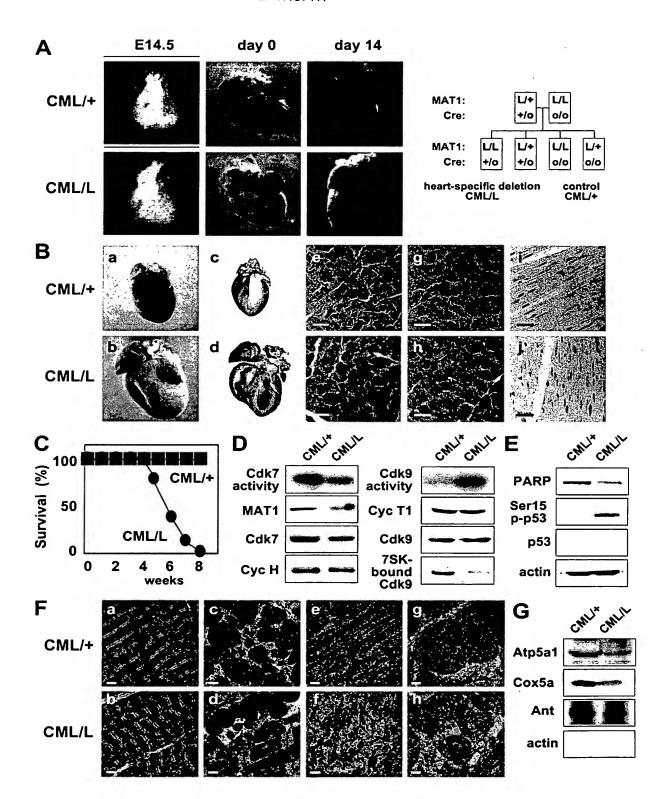
Title: MODULATORS OF Cdk9 AS A THERAPEUTIC TARGET



**FIG. 9** 

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**FIG. 10** 

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IN CARDIAC HYPERTROPHY



.3 -2 -1 0 1 2 3

## REPRESSED AT 4 WK BY CARDIOMYOCYTE-SPECIFIC DELETION OF MAT1:

a-oxoacid CoA transferase
a-cetyl-Coenzyme A dehydrogenase, short chain
BCL2/adenovirus E18 19 kDa-interacting protein 1, NIP3
bone morphogenetic protein 7
branched chain ketoacid dehydrogenase E1, beta
catherin 13
calcium channel, voltage-dependent, T type, aipha 1G
carnitine deficiency-associated gene expressed in ventricle 1
catechol-O-methyltransferase
citrate synthase
cut-like 1 (Drosophila)
cytochrome c oxidase, subunit VIIa 1
DEAD/H (Asp-Glu-Ala-Asp/His) box polypeptide 16
deleted in polyposis 1
dihydrolipoamide dehydrogenase
dodecencyl-Coenzyme A delta isomerase
electron transferring flavoprotein, aipha
enoyl coenzyme A hydratase, short chain, 1, mitochondrial
fibroblast activation protein
FKS06 binding protein 4 (59 kDa)
four and a half LIM domains 2
fumarate hydratase 1
G eiongation factor
gap junction membrane channel protein alpha 1
heat shock 10 kDa protein 1 (chaperonin 10)
heat shock protein, 60 kDa
histidine rich calcium binding protein
interferon activated gene 203
iroquois related homeobox 3 (Drosophila)
isocitrate dehydrogenase 3 (NAD+), gamma
isovateryl coenzyme A dehydrogenase
kit ligand iipin 1
iipon 1
iipon 1
iipocalin 7
metal response element binding transcription factor 2
metalidathonein 1
methylmalonyi-Coenzyme A mutase
mitochondrial ribosomal protein L12
mitochondrial ribosomal protein L34
myeloid feulkemia factor 1
myomesi 2
NADH dehydrogenase (ubiquinone) flavoprotein 2
p300/CBP-associated factor
peroxiredoxin 3
phosphofructokinase, liver, B-type
phospholipid transfer protein
phytanoyi-CoA hydroxylase
piasma membrane associated protein, S3-12
potassium voltage-gated channel, Shal-related family, 2
programmed cell death 8
prohibitin
prostaglandin D2 synthase (21 kDa, brain)
proteasome (prosome, macropain) 28 subunit, aipha
RAN guanine nucleotide release factor
retinoid X receptor gamma
sequestosome 1
stabultransferase 8 (alpha-2, 8-sialyltransferase) D retinoid X receptor gamma sequestosome 1 sialytransferase) D sialytransferase 8 (alpha-2, 8-sialytransferase) D thiolase/enoyi-Coenzyme A hydratase, beta subunit sirtuin 3 (silent mating type information regulation 2, homolog) 3 succinate dehydrogenase complex, subunit A succinate-Coenzyme A ligase, GDP-forming, beta subunit thyroid homone responsive SpOT14 homolog (Rattus) transcription elongation factor A (SII), 3 transforming growth factor, beta induced, 68 kDa translocator of inner mitochondrial membrane 44 ubiquinol-cytochrome c reductase core protein 1 vascular endothelial growth factor B

## INDUCED AT 4 WK BY CARDIOMYOCYTE-SPECIFIC DELETION OF MAT1:

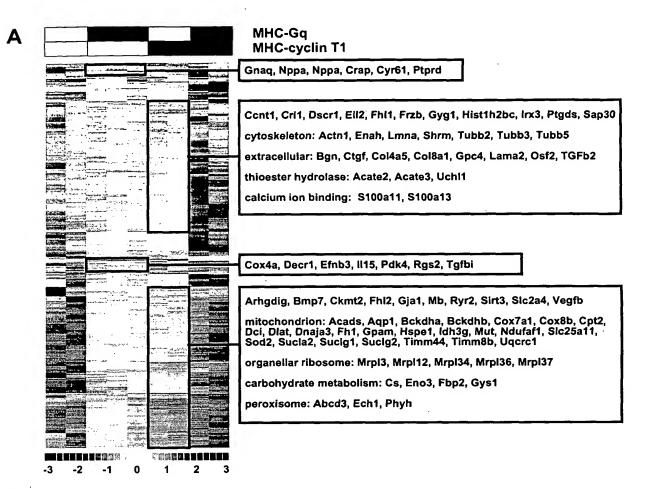
MAP kinase-interacting serine/threonine kinase 2 matrix gamma-carboxyglutamate (gla) protein mossin myosin, heavy polypeptide 7, cardiac muscle, beta myotrophin nestin neuturin Niemann Pick type C2 NS1-associated protein 1-like nuclear cap binding protain subunit 2, 20kDa nuclear protein 1 omithine decarboxylase antizyme inhibitor osteoblast specific factor 2 (fasciclin Hike) paraoxonase 2 POZ and Lift Momain 3 phosphofructokinese, platelet phospholidylinositol transfer protein 2 procollagen C-proteinase enhancer protein procollagen, type V, alpha 5 procollagen, type V, alpha 5 procollagen, type V, alpha 1 programmed cell death 6 interacting protein prostaglandin 12 (prostacyclin) synthese protein tyrosine phosphatase, non-receptor type 21 qualin 12 programmed cell death 6 interacting protein protein tyrosine phosphatase, non-receptor type 21 qualin 12 programmed cell death 6 interacting protein protein tyrosine phosphatase, non-receptor type 21 qualin 12 profession phosphatase, non-receptor type 21 qualin 12 profession phosphatase, non-receptor type 21 qualin 12 protein admit protein 4 RNA polymerase I associated factor, 53 kD S100 calcium binding protein A10 (calpactin) S100 calcium binding protein A10 (calpactin) S100 calcium binding protein A10 (calpactin) servited modular calcium binding protein A10 (calpactin) servite modular calcium binding protein A10 (calpactin) servited modular calcium 26S proteasome-associated pad 1 homolog
5' nucleotidase, ecto
a disintegrin and metalloproteinase domain 9
actinin, alpha 1
acyl-Coenzyme A thioesterase 2, mitochondrial
acyl-Coenzyme A thioesterase 3, mitochondrial
aldehyde dehydrogenase family 1, subfamily A1
annexin A1
annexin A3
ariadne homolog 2 (Drosophila)
biglycan MAP kinase-interacting serine/threonine kinase 2 matrix gamma-carboxyglutamate (gia) protein annexin A3
ariadne homolog 2 (Drosophila)
bigiycan
calcium and integrin binding 1 (caimyrin)
cardiac morphogenesis
cassin kinase 1, detta
CD24a antigen
CD81 antigen
CD81 antigen
CD81 antigen
chapronin subunit 8 (theta)
chloride intracellular channel 4 (mitochondrial)
chloride intracellular channel 4 (mitochondrial)
chondroitin sulfate proteoglycan 2
coagulation factor II (thrombin) receptor
connective tiesue growth factor
CREBBP/EP300 inhibitory protein 1
cyclin-dependent kinase inhibitor 1A (P21)
cysteine rich intestinal protein
cysteine rich protein
cytokine receptor-like factor 1
cytokine receptor-like factor 1
cytokine receptor-like factor 1
cytokine receptor-like factor 1
diaphorase 1 (MADH)
dihydropyrimidinase-like 3
elastin
enabled homolog (Drosophila)
epidermal growth factor pathway substrate 15
epithelial membrane protein 1
fibulin 2
follistatin-like
four and a half LIM domains 1 epithelial membrane protein 1
fibulin 2
follistatin-like
four and a half LIM domains 1
glutamine synthetase
glutathlone peroxidase 3
glycogenin 1
granulin
GrpE-like 1, mitochondrial
H3 histone, family 3B
heat shock 27kD protein 2
heat shock 27kD protein 2
heat shock 7k ba protein 4
heparin-binding spidermal growth factor
histone H3
HIV-1 Rev binding protein
hypoxia inducible factor 1, alpha subunit
IK cytokine
Inhibitor of DNA binding 2
insulin-like growth factor binding protein
rinsulin-like growth factor binding protein
integrin lapha 5 (fibronectin receptor aipha)
integrin beta 4
binding protein
integrin linked kinase
interferon-related developmental regulator 1
lamin A
low-density lipoprotein receptor-related protei lamin A low-density lipoprotein receptor-related protein 10 LPS-induced TN factor lysyl oxidase

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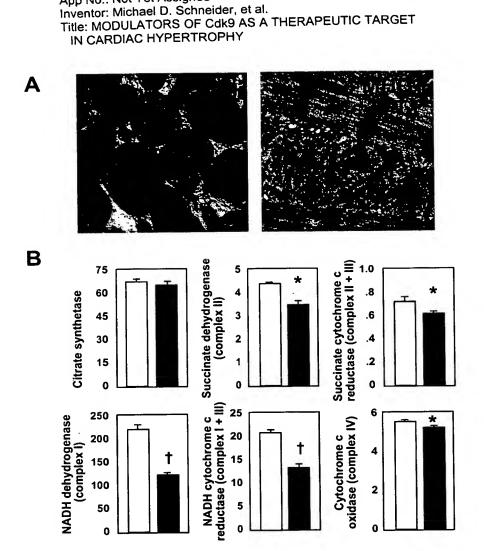
IN CARDIAC HYPERTROPHY



Genotype	Gq	cyclin T1
Common markers of cardiac hypertrophy		
ANP		6.29
BNP	3.57	1.43
MHC	0.84	0.45
MHC	8.32	1.15
skeletal -actin	6.49	0.99
SERCA2	0.77	0.34
ryanodine receptor	0.68	0.48
phospholamban	0.96	0.30
connexin-43	1.13	0.46 "
Hsp70	2.58	12.91
rispro	instant we will be a	
Cardiac-specific transcription factors	0.98	0.84
Nkx2.5	1.06	0.76
GATA-4		
MEF2C	1.02	0.82
Tbx5	0.89	0.98
SRF	1.09	1.03
Mitochondrial function		
PPAR coactivator-1	0.83	0.39
nuclear receptor factor-1	1.21	0.74
nuclear receptor factor-2	1.12	0.68
Ttranscription factor A, mitochondrial	0.96	0.53
PPAR	0.99	1.01
carnitine palmitoyltransferase 1	0.97	0.38
cytochrome C	0.86	0.5
cytochrome C oxidase Va (H)	1.03	0.74
cytochrome C oxidase VIa (H)	1.13	0.31
ATP synthase c	1.09	0.40
ATP synthase	0.82	0.44
adenosine nucleotide translocator-1	0.94	0.61
Sod2	0.75	0.39

В

**FIG. 12** 



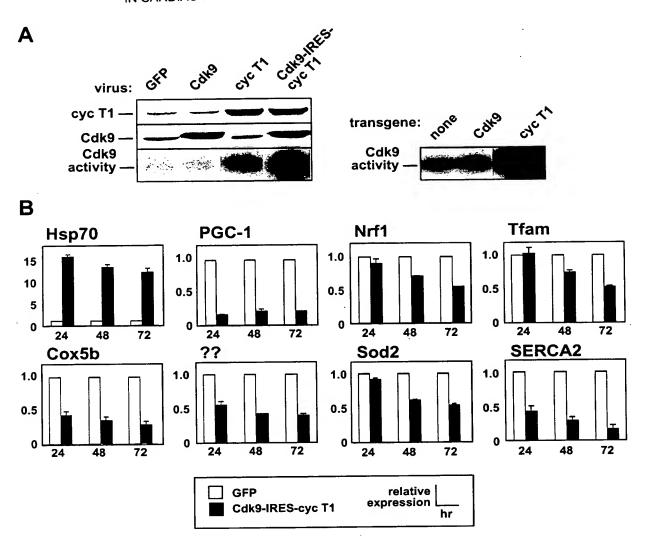
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**FIG. 13** 

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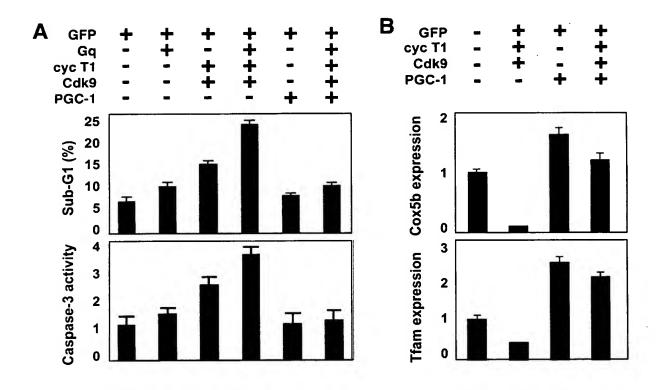
Title: MODULATORS OF Cdk9 AS A THERAPEUTIC TARGET



**FIG. 14** 

Inventor: Michael D. Schneider, et al.

Title: MODULATORS OF Cdk9 AS A THERAPEUTIC TARGET



**FIG. 15**